REMARKS

The present invention relates to articles of manufacture and formulations for the in vivo delivery of substantially water insoluble pharmacologically active agents (e.g., the anticancer drug paclitaxel) in nanoparticle form. Invention articles comprise a dry powder or liquid formulation comprising a solid core of amorphous, water insoluble drug nanoparticles coated with at least one protein, wherein the protein is albumin.

By the present communication, claim 73 has been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims (see, for example, page 23, lines 5-7; page 24, lines 20-23; and page 42, line 25 (with respect to the phrase "water insoluble drug"); and page 70, lines 29-31 and page 71, lines 4-6 (with respect to the phrase "solid core nanoparticles") of Applicants' specification). In view of the amendments submitted herewith, claims 101, 102 and 107 have been cancelled without prejudice.

Accordingly, claims 73-75, 103-105, 108 and 122-133 remain pending. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2.

Rejection under 35 U.S.C. §102(e) over Violante

The rejection of claims 73, 101-103, 107, 108 and 122-132 under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,741,522 (Violante), is respectfully traversed.

Applicants' invention, as defined for example by amended claim 73, distinguishes over Violante at least by requiring an article of manufacture comprising a dry powder or liquid formulation of a water insoluble drug and at least one protein. Invention formulations comprise a solid core of amorphous, water insoluble drug nanoparticles coated with protein, wherein the protein is albumin. Violante does not disclose or suggest such articles or formulations. Indeed,

Violante is clearly very different from the articles contemplated by the present claims as Violante is directed to water soluble, iodinated diagnostic ultrasound agents that contain gaseous bubbles.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. § 102(b) over Mathiowitz

The rejection of claims 73, 101-103, 107, 108 and 122-132 under 35 U.S.C. §102(b), as allegedly being anticipated by U.S. Patent No. 5,721,961 (Mathiowitz), is respectfully traversed.

Applicants' invention, as defined for example by amended claim 73, distinguishes over Mathiowitz at least by requiring an article of manufacture comprising a dry powder or liquid formulation of a water insoluble drug and at least one protein. Invention formulations comprise a solid core of amorphous, water insoluble drug nanoparticles coated with protein, wherein the protein is albumin. Mathiowitz does not disclose or suggest such articles or formulations. Instead, Mathiowitz discloses microspheres encapsulated by hydrophobic proteins (e.g., prolamine). Those of skill in the art readily recognize that the hydrophobic proteins suggested by Mathiowitz are very different than the protein required by the present claims, i.e., albumin.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. §102(e) over End

The rejection of claims 73, 102, 107, 108 and 122-132 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,700,471 (End), is respectfully traversed.

Applicants' invention, as defined for example by amended claim 73, distinguishes over End at least by requiring an article of manufacture comprising a dry powder or liquid formulation of a water insoluble drug and at least one protein. Invention formulations comprise

a solid core of amorphous, water insoluble drug nanoparticles coated with protein, wherein the protein is albumin. End does not disclose or suggest such articles or formulations. Instead, End is directed to the preparation of particulate material as a fine colloid, employing agents which are very different than the albumin required by the present claims, e.g., gelatins (see, for example, col. 2, lines 43-51 of End). Those of skill in the art readily recognize that the colloidal agents contemplated by End are substantially different than the albumin required by the present claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

The rejection of claims 73, 74, 104 and 133 under 35 U.S.C. § 102(e) [sic—103(a)?] as allegedly being anticipated by [sic—obvious over?] Violante in view of U.S. Patent No. 6,143,276 (Unger *et al.*) is respectfully traversed. While the rejection is presented as a rejection under 35 U.S.C. § 102(e), it is presumed that this rejection is intended to be asserted under 35 U.S.C. § 103(a), based on the discussion which precedes and follows the actual rejection. If this assumption is incorrect, clarification on the record is respectfully requested.

Applicants' invention, as defined for example by amended claim 73, distinguishes over Violante at least by requiring an article of manufacture comprising a dry powder or liquid formulation of a water insoluble drug and at least one protein. Invention formulations comprise a solid core of amorphous, water insoluble drug nanoparticles coated with protein, wherein the protein is albumin. As discussed above, Violante does not disclose or suggest such formulations.

Further reliance on Unger is unable to cure the deficiencies of Violante. No motivation has been provided, absent Applicants' specification, to combine the asserted references. Such use of Applicants' disclosure is clearly improper.

Even if combination of Violante and Unger were proper, the combination would not lead one of skill in the art to arrive at the present invention. Whereas Violante relates to water

soluble, iodinated diagnostic ultrasound agents that contain gaseous bubbles, Unger relates to methods for delivery of bioactive agents using compositions comprising the bioactive agent and a gaseous precursor. As a result, one attempting to combine the teachings of the asserted references would perhaps achieve an alternate method to deliver the ultrasound agents of Violante, or the bioactive agent of Unger, but one would definitely not obtain a nanoparticle coated with protein as required by the present claims.

The rejection of claim 105 under 35 U.S.C. § 103(a) as allegedly being obvious over Violante in view of Unger, and further in view of U.S. Patent No. 5,731,355 (Jones *et al.*), is respectfully traversed.

Applicants' invention, as defined for example by amended claim 73, distinguishes over Violante at least by requiring an article of manufacture comprising a dry powder or liquid formulation of a water insoluble drug and at least one protein. Invention formulations comprise a solid core of amorphous, water insoluble drug nanoparticles coated with protein, wherein the protein is albumin. As discussed above, Violante does not disclose or suggest such formulations. As also discussed above, further reliance on Unger is unable to cure the deficiencies of Violante. No motivation has been provided, absent Applicants' specification, to combine the asserted references. Such use of Applicants' disclosure is clearly improper.

Still further reliance on Jones is unable to cure the deficiencies of Violante in view of Unger. No motivation has been provided, absent Applicants' specification, to combine the asserted references. Such use of Applicants' disclosure is clearly improper.

Even if combination of Violante, Unger and Jones were proper, the combination would not lead one of skill in the art to arrive at the present invention. Whereas Violante relates to water soluble, iodinated diagnostic ultrasound agents that contain gaseous bubbles, and Unger relates to methods for delivery of bioactive agents using compositions comprising the bioactive agent and a gaseous precursor, Jones relates to methods of producing anaesthesia employing oil-

in-water emulsions of a defined agent. As a result, one attempting to combine the teachings of the asserted references would perhaps achieve an alternate method to deliver the anaesthetic of Jones, but would not obtain a nanoparticle coated with protein as required by the present claims.

The rejection of claims 73-75, 101-104, 107, 108 and 122-123 under 35 U.S.C. § 102(b) [sic—103(a)?] as allegedly being anticipated by [sic—obvious over?] U.S. Patent No. 5,439,686 (Desai *et al.*) in view of U.S. Patent No. 6,197,349 (Westesen *et al.*) is respectfully traversed. While the rejection is presented as a rejection under 35 U.S.C. § 102(b), it is presumed that this rejection is intended to be asserted under 35 U.S.C. § 103(a), based on the discussion which precedes and follows the actual rejection. If this assumption is incorrect, clarification on the record is respectfully requested.

Applicants' invention, as defined for example by amended claim 73, distinguishes over Desai at least by requiring an article of manufacture comprising a dry powder or liquid formulation of a water insoluble drug and at least one protein. Invention formulations comprise a solid core of amorphous, water insoluble drug nanoparticles coated with protein, wherein the protein is albumin. Desai does not disclose or suggest such articles or formulations.

Further reliance on Westesen is unable to cure the deficiencies of Desai. No motivation has been provided, absent Applicants' specification, to combine the asserted references. Such use of Applicants' disclosure is clearly improper.

Even if combination of Desai and Westesen were proper, the combination would not lead one of skill in the art to arrive at the present invention. Whereas Desai relates to particles coated with protein, Westesen relates to particles comprising a supercooled melt of a poorly soluble substance and a stabilizing agent. As readily recognized by those of skill in the art, particles of supercooled melts are very different in size, shape and compositions from the particles disclosed by Desai, or the particles contemplated by the present claims. Furthermore, to work with melts of a poorly soluble substance, one would, of necessity, have to work at temperatures sufficient to

achieve a melt, which elevated temperatures would clearly be incompatible with delicate structures such as proteins. As a result, one attempting to combine the teachings of the asserted references would achieve a very different article than contemplated by the present claims.

Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph

The rejection of claims 75 and 102 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is respectfully traversed. With respect to claim 75, Applicants respectfully disagree with the Examiner's assertion that "the base claim states that the particles are coated with albumin and such a coating would be within the scope of surfactant." (See sentence bridging pages 7-8 of the Office Action). No basis has been provided for the Examiner's assertion. Indeed, it is submitted to be clear to those of skill in the art that albumin is a protein, and not a surfactant. See, for example, the Handbook of Excipients – under the heading "Surfactants," which lists several surfactant compounds, none of which are the protein albumin. Furthermore, the Examiner's attention is directed specifically to pages 5-6 of the above-identified reference (copy provided herewith for the Examiner's convenience), which describes albumin as a stabilizing/therapeutic agent, not a surfactant.

With respect to claim 102, this rejection has been rendered moot by the cancellation of this claim.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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By: _____

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Enclosure